DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

William C. Weldon
Chairman of the Board and Chief Executive Officer
Johnson & Johnson
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

RE: NDA# 21-692
ULTRAM® ER (tramadol HCl) Extended-Release Tablets
MACMIS # 17464

WARNING LETTER

Dear Mr. Weldon:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a consumer webcast video titled "Making Sure Your Relationships Aren't Pained When You're In Chronic Pain" (webcast) [02U0307B] for ULTRAM® ER (tramadol HCl) Extended-Release Tablets (Ultram ER) submitted by Johnson & Johnson on behalf of Ortho-McNeil-Janssen Pharmaceuticals, Inc. (hereinafter collectively referred to as Johnson & Johnson) under cover of Form FDA 2253 and also available on the webpage www.painawareness.org.[1] The webcast for Ultram ER is false or misleading because it omits and minimizes the serious risks of the drug and overstates the efficacy of Ultram ER, asserting that it has benefits that have not been demonstrated. The promotional material thus misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & (n); 321(n). *Cf*. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i) & (e)(7)(viii). This webcast is concerning from a public health perspective because it suggests that Ultram ER is safer and more effective than has been demonstrated by substantial evidence or substantial clinical experience.

Background

According to its FDA-approved product labeling (PI), Ultram ER is indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.

Ultram ER is associated with the serious risks of potent narcotics, some of which are potentially fatal. It is contraindicated in patients who have previously demonstrated hypersensitivity to tramadol, any of Ultram ER's other components, or other opioids. Ultram ER is also contraindicated in any situation where other opioids are contraindicated, including acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs, due to the risk of worsening central nervous system (CNS) and respiratory depression.

[1] Available at: http://content.painawareness.org/media/player/index.htm; last accessed April 8, 2009.

The PI also includes warnings regarding the risk of seizures, the risk of suicide, the potentially fatal risks of serotonin syndrome and anaphylactoid reactions, respiratory depression, interaction with CNS depressants, increased intracranial pressure or head trauma, use in ambulatory patients, use with MAO inhibitors and serotonin re-uptake inhibitors, withdrawal symptoms, misuse, abuse and diversion of opioids, drug abuse and addiction, and the potentially fatal risk of overdosage.

Additionally, the PI contains precautions regarding patients with acute abdominal condition and use in renal and hepatic disease. Furthermore, the PI states that the most frequently reported adverse events in patients taking Ultram ER were dizziness, nausea, constipation, headache, and drowsiness.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal material facts in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

The webcast fails to convey any risks specific to Ultram ER during the testimonial portion of the video, which encompasses the first six minutes of the video's seven-minute running time. While the video prominently presents efficacy claims about Ultram ER during this six-minute testimonial portion, the only specific risk information presented is relegated to the end of the video, where it is unlikely to draw the viewer's attention. Furthermore, this information is presented in a telescript format, with rapidly scrolling text in small type font, and with no accompanying audio presentation. The presentation of this risk information lacks comparable prominence to the benefit claims contained in the testimonial portion of the webcast.

Furthermore, this disclosure of risk information omits serious risks associated with Ultram ER. Specifically, the telescript fails to convey that "Ultram ER is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. Ultram ER may worsen central nervous system and respiratory depression in these patients." Additionally, it fails to convey the warning that "ULTRAM ER should be used with caution in patients with increased intracranial pressure or head injury."

Furthermore, this telescript presentation minimizes some of the serious risks associated with Ultram ER. It contains a statement informing patients not to take Ultram ER if they have previously experienced an allergic reaction to tramadol, codeine, or other opioids. However, it fails to inform patients that serious anaphylactic reactions can occur even if patients have never taken tramadol. Additionally, it minimizes the risk of seizures in patients on Ultram ER therapy. The telescript states that patients with epilepsy or a history of seizures have an increased risk of convulsions while on Ultram ER therapy, but it fails to communicate that, according to the Warnings section of the PI, "Risk of convulsions may also increase in patients…with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections)."

Moreover, the risk presentation minimizes the risk of interaction with CNS depressants for patients on Ultram ER therapy. The telescript states, "Taking more than the recommended dose of ULTRAM® ER, alone or in combination with alcohol or medications such as tranquilizers, hypnotics or other opioids, can cause respiratory depression, seizures, overdose and possibly death." However, it does not communicate that these risks exist with Ultram ER **at all dosage levels**, not only when taken at a greater than recommended dose, as well as in patients taking alcohol, anesthetic agents, narcotics, or phenothiazines. According to the Warnings section of the PI, "ULTRAM ER should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. ULTRAM ER increases the risk of CNS and respiratory depression in these patients."

The overall effect of this presentation undermines the communication of important risk information, minimizing the risks associated with Ultram ER and misleadingly suggesting that Ultram ER is safer than has been demonstrated.

Overstatement of Efficacy

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The webcast presents statements made by Dr. Michael Schatman, Assistant Professor of Family Medicine at Pacific Northwest University of Health Sciences College of Osteopathic Medicine, and Olympic Gold Medalist Nikki Stone about the consequences of chronic pain and the impact of treatment with Ultram ER.

Dr. Schatman's statements include the following:

- "[I]f you are one of the estimated fifty million Americans suffering from persistent chronic pain, stress caused by persistent chronic pain may be affecting your relationships more than you think."
- "In a new online survey of 500 American adults suffering from chronic pain approximately 68% agree that their chronic pain causes stress in their families. Moreover, 75% of people 31 to 40 years old stated that their chronic pain has had a negative effect on their relationship with their spouse or partner."
- "Chronic pain can cause stress, which may lead to a sense of hopelessness or depression. According to the Mayo Clinic, some research has even shown that pain and depression actually share common pathways from the regions of the brain associated with emotion."
- "…[S]leep disturbances are not uncommon for patients suffering from persistent chronic pain …. Whether it causes arguments, lack of intimacy, or loss of sleep there's no doubt that chronic pain can affect our relationships"
- "If you think that loss of sleep or poor sleep quality due to persistent chronic pain is affecting your relationships, you may want to speak with your healthcare professional about your options, which may include prescription medication to help you manage your chronic pain throughout the night."

This final statement is followed by an announcer stating, “Also, you can visit www.ULTRAM-ER.com” while the screen displays the accompanying SUPER “www.ULTRAM-ER.com.”

Ms. Stone’s statements include the following (emphasis added):

- “The thought of being in severe chronic pain the rest of my life, let alone experiencing the pain itself, made me feel a sense of hopelessness. The hopelessness grew into a feeling of depression and as a result, my relationships with my parents, my friends, and my boyfriend became strained. I was not interested in group outings and ended up losing some friends …. I just wasn’t my same happy self and no one seemed to understand.”
- “I worked with my doctors to effectively manage my chronic pain, which in turn, gave me my hope back …. I’m happy to say that despite our hardship I’m now married to that boyfriend who at the time I had alienated from my life.”
- “After my Olympic career had ended, I still experienced persistent chronic pain on a daily basis. **My chronic pain even woke me up throughout the night. And as anyone knows, if you don’t get a proper night’s sleep, it can become difficult to function during the day, let alone be pleasant to friends and family.** My battle with chronic pain, and my struggle to properly manage my relationships are something that I will always have to work at, but it’s something that’s worth it to me.”
- “**Because my chronic pain was waking me up throughout the night, I worked with my doctors and found a medication called Ultram ER**, that provides management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time. Ultram ER not only helped to manage my chronic pain, but **because Ultram ER is a 24-hour treatment, I no longer found myself waking up due to chronic pain**. This was and is important to my overall chronic pain management program, because **sleep is a critical factor in my overall mood, which affects my relationships.”**

Throughout the webcast, the following statement is displayed to the right of the screen and below the screen: “For more information, visit www.ULTRAM-ER.com”.

These presentations greatly misrepresent what is known about the efficacy of Ultram ER. First, the webcast implies that an outcome of treatment with Ultram ER is a positive effect on patients’ overall mood (including the alleviation of depression) and interpersonal relationships. FDA is not aware of any evidence to support such effects of Ultram ER treatment. Second, the webcast misleadingly implies that patients treated with the drug will experience an improvement in their sleep quality. The webcast cites no references in support of these claims and we are not aware of substantial evidence or substantial clinical experience to support this effect of Ultram ER. Claims regarding sleep-related outcomes require positive findings using objective tests of sleep such as polysomnography. If you do, in fact, have data to support these claims, you should submit them to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the webcast misbrands Ultram ER in violation of the Act, 21 U.S.C. 352(a) & (n); 321(n). *Cf*. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i) & (e)(7)(viii).

DDMAC requests that Johnson & Johnson immediately cease the dissemination of violative promotional materials for Ultram ER such as those described above. Please submit a written response to this letter on or before May 27, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for Ultram ER as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS# 17464 in addition to the NDA number. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Ultram ER comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Abrams

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